Dynamic changes in the human methylome during differentiation.

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Public Summary:
All of the cells in our bodies, except for some cells in the immune system, have the same DNA sequence. Each cell type has a different set of active genes which make it function correctly. For example, muscle cells make myosin, which allows muscles to contract, while cells in the pancreas do not make myosin, but rather make insulin to regulate blood glucose levels. "Epigenetics" refers to the processes that affect the activity of the genome without changing the DNA (genetic) sequence. One type of epigenetic process is a modifications of DNA called methylation. The "C"s in the DNA sequence can be methylated, which makes them look different to the regulatory molecules that bind to DNA and cause genes to be active. Usually, methylation of C's in genes turns those genes off. We wanted to understand how human pluripotent stem cells change the methylation pattern of their DNA when they transform themselves into differentiated cells that express a very different group of genes. We sequenced the entire "methylome" of human ES cells before and after they differentiated. This is the first time that the human developmental methylome had been completely sequenced. Our effort was equivalent to sequencing the whole human genome, twice for each cell type, for a total of 6 complete genome sequences. We found amazing changes in the methylation of genes as the cells differentiated. Almost all of them were unexpected, so we now have opened the door to a whole new scientific field- understanding human development and disease by studying the details of the epigenome.

Scientific Abstract:
DNA methylation is a critical epigenetic regulator in mammalian development. Here, we present a whole-genome comparative view of DNA methylation using bisulfite sequencing of three cultured cell types representing progressive stages of differentiation: human embryonic stem cells (hESCs), a fibroblastic differentiated derivative of the hESCs, and neonatal fibroblasts. As a reference, we compared our maps with a methylome map of a fully differentiated adult cell type, mature peripheral blood mononuclear cells (monocytes). We observed many notable common and cell-type-specific features among all cell types. Promoter hypomethylation (both CG and CA) and higher levels of gene body methylation were positively correlated with transcription in all cell types. Exons were more highly methylated than introns, and sharp transitions of methylation occurred at exon-intron boundaries, suggesting a role for differential methylation in transcript splicing. Developmental stage was reflected in both the level of global methylation and extent of non-CpG methylation, with hESC highest, fibroblasts intermediate, and monocytes lowest. Differentiation-associated differential methylation profiles were observed for developmentally regulated genes, including the HOX clusters, other homeobox transcription factors, and pluripotence-associated genes such as POU5F1, TCF3, and KLF4. Our results highlight the value of high-resolution methylation maps, in conjunction with other systems-level analyses, for investigation of previously undetectable developmental regulatory mechanisms.

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